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WO 2004/000781 A2

(54) Title: NITROOXYDERIVATIVES OF CYCLOOXYGENASE-2 INHIBITORS

(57) Abstract: New compounds able to release COX-2 inhibitors and NO having formula (I):M-T-YA-NO?2#191(I) for the treatment and/or prophylaxis of inflammatory processes.

TITLE OF THE INVENTION
"NITROOXYDERIVATIVES OF CYCLOOXYGENASE-2 INHIBITORS"

5 The present invention relates to nitro-derivatives of cyclooxygenase-2 inhibitors (hereafter referred to as COX-2 inhibitors), pharmaceutical compositions containing them and their use for the treatment and/or prophylaxis of inflammations, such as for example arthritis, osteoarthritis, rheumatoid arthritis, dysmenorrhea, pain and fever, gastrointestinal and cardiovascular disorders, rheumatic diseases, neoplasia and
10 Alzheimer's disease, for mitigating or removing the known side-effects of COX-2 inhibitors and for treating and/or preventing disorders resulting from elevated levels of cyclooxygenase-2.

Cyclooxygenase is the enzyme that converts arachidonic acid into prostanoids. Further to the development of non-steroidal anti-inflammatory drugs (NSAIDs), it became easily clear that for said compounds there is a strict and direct relationship between activity and toxicity. In fact, even though they inhibit the cyclooxygenase activity, preventing the formation of pro-algogen/inflammatory prostanoids, on the other hand they give rise to a reduction of protective prostanoids, so that injury to the gastrointestinal tract is the obvious result. Further studies have demonstrated that there are two different types of cyclooxygenase enzymes: the so called constitutive form (COX-1), responsible for the production of the protective prostanoids, and the inducible form (COX-2), producing the pro-algogen/inflammatory prostanoids (J. R. Vane et al., Ann. Rev. Pharmacol. Toxicol. 1998, 38:97 – 120). Therefore, it has been postulated that the NSAIDs anti-inflammatory effects are mediated by COX-2 inhibition, whereas their side effects are due to the inhibition of COX-1. However, it is known that COX-1 enzyme is physiologically concerned with the generation of prostaglandins exhibiting a protective effect on gastric mucous membrane, at renal and gastrointestinal level as well as on the platelets aggregation. Hence anti-inflammatory drugs specifically inhibiting COX-2 without inhibition of COX-1 should be free from the side effects associated with conventional NSAID. It has been then verified that to a patient taking a selective COX-2 inhibitor also a NSAID should be administered for having cardioprotective action; however, in this way he will not be free from gastrointestinal inconveniences. In the same way, switching from a non-steroidal anti-inflammatory drug to a selective COX-2 inhibitor, the cardioprotective activity will be lost, gaining however in anti-arthritis properties. On the ground of these concepts, selective COX-2

inhibitors have been developed having the desired therapeutic profile of an anti-inflammatory drug without the adverse effects commonly associated with the inhibition of COX-1. However, all these compounds have demonstrated to not be free from side effects, as for example dyspepsia and gastropathy, as well as gastrointestinal and cardiovascular risks (Mohammed et al., N. Engl. J. Med., 340(25)2005, 1999). Notwithstanding the continuous development of always new COX-2 inhibitors, the problem of their side effects is still unresolved. So it has been reported about the potential risk of cardiovascular events, acute colitis, gastrointestinal haemorrhage, allergic vasculitis, intestinal diseases.

10 In WO 01/45703 nitrosated and nitrosylated cyclooxygenase-2 inhibitors as well as compositions comprising at least one of these new inhibitors, and, optionally, at least one compound that donates, transfers or releases nitric oxide are described. In said application it is stated that the adverse effects of the known COX-2 inhibitors can be diminished or prevented if said inhibitors contain at least a nitrite, nitrate, thionitrite or thionitrate group. In particular, in this patent were exemplified the preparations of compounds containing the $-O-NO_2$ group (nitrosated cyclooxygenase-2 inhibitors) directly linked to the COX-2 inhibitor moiety and the synthesis of COX-2 inhibitors derivatives containing the $-S-NO$ group (nitrosylated cyclooxygenase-2 inhibitors) indirectly linked to the precursor drugs. inhibitors.

15 It was an object of the present invention to provide new derivatives of cyclooxygenase-2 inhibitors not having the disadvantages mentioned above and that are transformed in vivo in compounds with enhanced COX-2 inhibiting activity and that release molecules able to modulate the bioavailability of nitrogen oxide so as to reduce or resolve the problems at cardiovascular and/or gastrointestinal level and to obtain a synergic action between COX-2 molecule and nitric oxide.

20 It was an object of the present invention to provide new derivatives of cyclooxygenase-2 inhibitors not having the disadvantages mentioned above and that are transformed in vivo in compounds with enhanced COX-2 inhibiting activity and that release molecules able to modulate the bioavailability of nitrogen oxide so as to reduce or resolve the problems at cardiovascular and/or gastrointestinal level and to obtain a synergic action between COX-2 molecule and nitric oxide.

25

Object of the present invention are compounds or salts thereof with enhanced pharmacological profile which are able to release COX-2 inhibitors and NO (nitrogen oxide) under conditions and according to the parameters set up in test 1 described below, having the general formula (I)



wherein

M-T is the residue of a COX-2 selective inhibitor, in which T = $-SO_2NH-$, $-SO_2NR-$, $-(CO)-$, $-O-$, $-S-$, $-NH-$, $-N(SO_2R)-$, R being alkyl with 1-10 carbon atoms, preferably

methyl, wherein the COX-2 selective inhibitor, M-TH or M-TOH, has to meet test 2 described below;

$Y_A = -(B)_{b0}-(C)_{c0}$ wherein:

b0 e c0 are the integers 1 or 0, with the proviso that b0 and c0 cannot be 5 simultaneously 0,

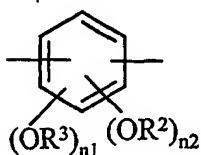
$B = -T_B-X_2-T_{B1}-$, in which:

$T_B = CO$ or X , wherein $X = O, S, NH, NR$, and R is as defined above, T_B is CO when T is $-SO_2NH-$, $-SO_2NR-$, $-O-$, $-S-$, $-NH-$, $-N(SO_2R)-$, T_B is X when T is $-CO-$;

$T_{B1} = CO$ or X , in which X is as defined above;

10 X_2 is a divalent radical and is selected from the following compounds:

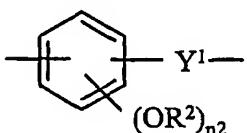
a)



wherein:

15 n1 and n2 are integers 0 or 1; R^2 and R^3 are independently selected from H or CH_3 ;

b)

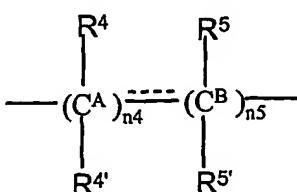


wherein:

n2 and R^2 are as above defined;

20 Y^1 is $-CH_2-CH_2-$ or $-CH=CH-(CH_2)_{n2'}$ wherein $n2'$ is an integer 0 or 1;

c)



wherein:

25 n4 is an integer from 1 to 20 and n5 is an integer from 0 to 20, R^4 and R^4' R^5 and R^5' are independently selected from H, CH_3 , OH, NH_2 , $NHCOCH_3$, $COOH$; when the bond between the C^A and C^B carbons is a double bond R^4 and R^5 or R^4' and R^5' are absent;

C is the bivalent radical $-T_C-Y-$, wherein:

$T_C = CO$, X wherein X is as defined above, or $-(CH_2)_{n6}OC(O)-$ wherein $n6$ is an integer from 1 to 20, preferably $n6$ is 1;

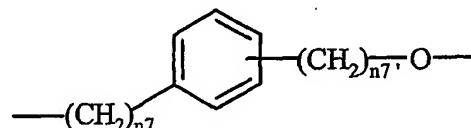
Y is a bivalent radical having the following meanings:

d) $-R^1O-$, in which R^1 is:

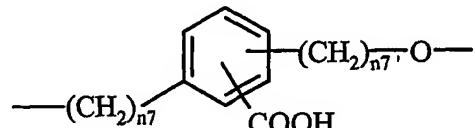
5 - straight or branched C_1-C_{20} -alkylene eventually containing one or more heteroatoms selected from oxygen, nitrogen, sulphur, or one or more groups $-O(CO)-$, $-NH(CO)-$, $-S(CO)-$, eventually substituted with one or more of the following groups $-OH$, $-SH$, $-NH_2$, $-NHCOR^6$, in which R^6 is straight or branched C_1-C_{10} -alkyl, preferably CH_3 ;

10 - cycloalkylene containing from 5 to 7 carbon atoms into cycloalkylene ring, wherein one or more carbon atoms can be replaced by heteroatoms selected from nitrogen, oxygen or sulphur, and the ring can be substituted with side chains R^8 , R^8 being as defined above;

e)

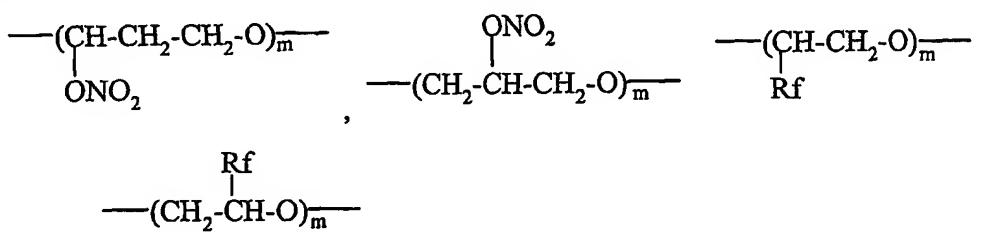


15 f)



wherein $n7$ is an integer from 0 to 20, and $n7'$ is an integer from 1 to 20;

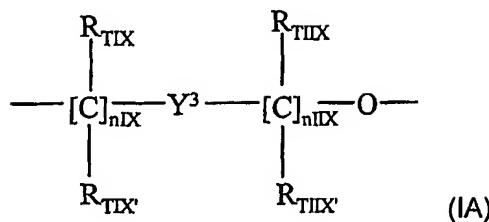
g)



20

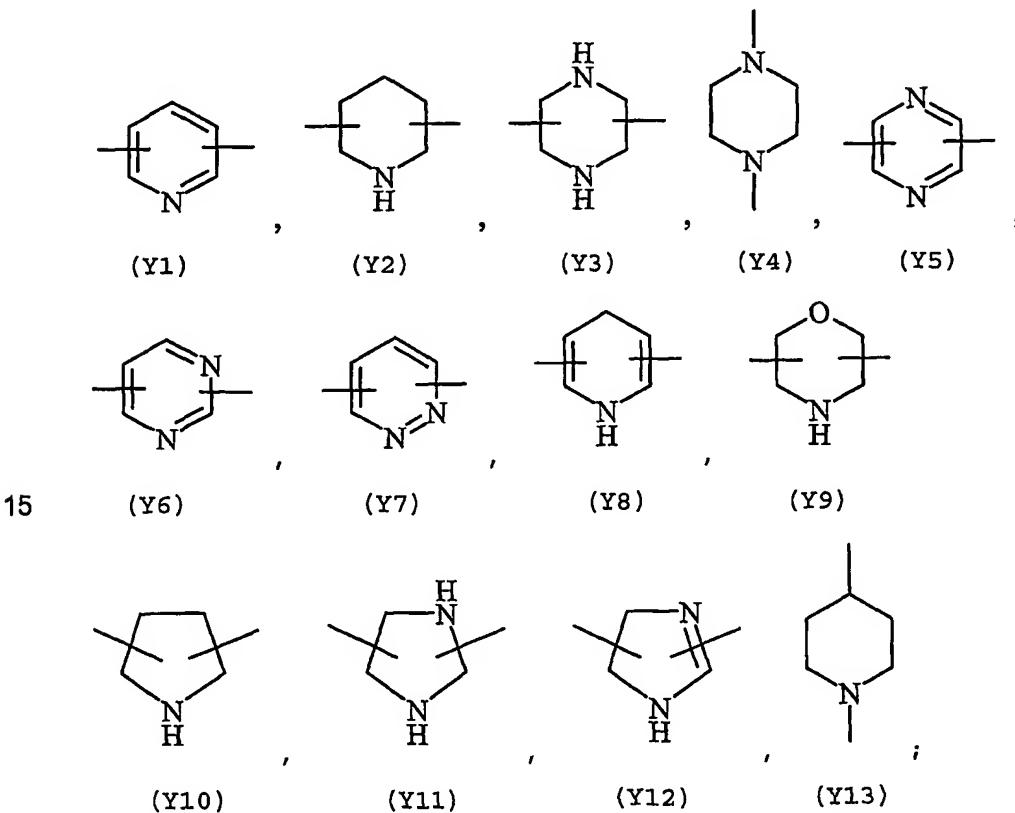
wherein m is an integer from 1 to 6, preferably from 1 to 4, Rf is a hydrogen atom or CH_3 ;

h)



wherein:

5 nIX is an integer from 0 to 10, preferably from 1 to 5;
 nIIX is an integer from 1 to 10, preferably from 1 to 5;
 R_{TIX} , $R_{TIX'}$, R_{TIIX} , $R_{TIIX'}$, are the same or different, and are H or straight or branched C₁-C₄-alkyl, preferably R_{TIX} , $R_{TIX'}$, R_{TIIX} , $R_{TIIX'}$ are H;
 Y^3 is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulphur, and selected from
 10 containing one or more heteroatoms selected from nitrogen, oxygen, sulphur, and selected from



with the proviso that:

when b0 = 0, c0 = 1 and T = -SO₂NH-, -SO₂NR-, -O-, -S-, -NH-, -N(SO₂R)- wherein R is
 20 as defined above, then T_C = (CO) or -(CH₂)_nO(CO);

when $b_0 = 0$, $c_0 = 1$ and $T = CO$ then $T_c = X$ wherein X is as defined above;

when $b_0 = 1$ and $T = -SO_2NH-$, $-SO_2NR-$, $-O-, -S-, -NH-, -N(SO_2R)-$ wherein R is as defined above, then $T_B = CO$;

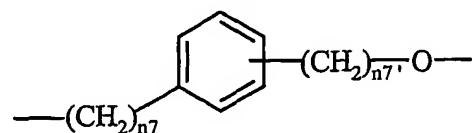
when $b_0 = 1$ and $T = CO$ then $T_B = X$ wherein X is as defined above;

5 when $b_0 = 1$, $c_0 = 1$ and $T_{B1} = CO$ then $T_c = X$ wherein X is as above defined;

when $b_0 = 1$, $c_0 = 1$ and $T_{B1} = X$, wherein X is as above defined, then $T_c = (CO)$;

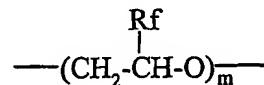
when $b_0 = 1$, $c_0 = 0$ the T_{B1} has only the meaning of $-O-$.

Preferred compounds of formula (I) are those wherein $b_0 = 0$, $c_0 = 1$, T and T_c are as defined in claim 1, Y is a straight C_1-C_6 alkylene or



10

wherein n_7 is 0 or 1, and n_7' is 1 or 2, or



wherein m is 2, Rf is hydrogen.

Particularly preferred compounds of formula (I) are those wherein $b_0 = 0$, $c_0 = 1$,

15 $T = -N(SO_2R)-$, $T_c = CO$ or $-(CH_2)_{n_6}O(CO)-$ wherein $n_6 = 1$ and $R = CH_3$ and those wherein $b_0 = 0$, $c_0 = 1$, $T = -SO_2NH-$ and $T_c = CO$ or $-(CH_2)_{n_6}O(CO)-$ wherein $n_6 = 1$.

Object of the present invention are also pharmaceutical compositions comprising at least a nitro-derivative of cyclooxygenase-2 inhibitors in combination with a pharmaceutically acceptable vehicle and their use in the treatment and/or prophylaxis 20 of inflammatory and cardiovascular disorders, arthritis, rheumatoid arthritis, dysmenhorrea, fever, pain, for treating and/or preventing disorders due to cyclooxygenase-2 elevated levels and for reducing or eliminating the well-known side effects of COX-2 inhibitors.

Test 1

25 Assay for COX-1 and COX-2 activities of the compounds of the invention.

To a rat liver isolated homogenate in potassium chloride (1,15 %) and phosphate buffer (0,1 M, pH 7.4) the compounds under examination were added (dissolved in DMSO 1%) at the 0,5 mM end concentration in homogenate, and the homogenate was maintained at room temperature for 30 minutes, then it was centrifugated (2000 rpm, 5 min) and in surnatant the COX-2 and COX-1 activities as well as the amount of NO released were determined according to the methods described here below.

1-1) In vitro evaluation of COX-2 and COX-1 activities (Human Whole Blood Assays)

The experiments have been carried out according to the procedure described by D. Riendeau et al., The Journal of Pharmacology and Experimental Therapeutics 296:558-566, 2001.

5 For the evaluation of COX-2 activity, human blood was collected from volunteers, heparin was added (19 U/ml) and several aliquots of 500 µl were incubated with LPS (100 µg/ml) and with 2 µl of solutions (DMSO 1%) of the compounds under examination at different concentrations using 3-fold serial dilutions (1:10, 1:100, 1:1000 e 1:10000) of the above described surnatant or with 2 µl vehicle (DMSO), for 24 h at
10 37°C. COX-2 activity in the samples has been measured in the plasma after deproteination as PGE2 concentration by radioimmunoassay (Amersham, Oakville, Ontario, Canada).

For the COX-1 assay, an aliquot of 500 µl of human blood was mixed with 2 µl of solutions (DMSO 1%) of the compounds at different concentrations using 3-fold serial dilutions (1:10 1:100 1:1000 and 1:10000) of the above described surnatant or with 2 µl vehicle (DMSO) and blood was allowed to clot for 1 h at 37°C.
15

COX-1 activity in the samples has been determined in the serum after deproteination as TXB2 levels using an enzyme immunoassay (Cayman Chemicals, Ann Arbor, MI).

1-2) Determination of NO release by chemiluminescence

20 An aliquot of the above described surnatant (100 µl) was injected in the reaction chamber of the analyzer containing a reductive solution consisting of glacial acetic acid and potassium iodide. Under these conditions, the nitrates/nitrites present in the sample are converted in NO which is then detected after its reaction with ozone. This reaction produces light, that is detected by photomultipliers and the recorded signal, proportional to the amount of emitted light, allows to quantify nitrates/nitrites present in
25 the sample. For the quantitative determination of the released NO, reference is made to a standard curve obtained with scalar nitrite concentrations.

The compounds meet test 1 when the ratio between COX-1 inhibiting activity and COX-2 inhibiting activity, expressed as IC₅₀, is greater than or equal to 5 and release
30 NO in amounts that can be detected by instrument, that is at a concentration equal to or greater than 0,1 µM.

Test 2

Assay for COX-1 and COX-2 activity of the precursor compounds according to the HWBA method (Human Whole Blood Assays)

The experiments have been carried out using identical procedures as reported by D. Riendeau et al., The Journal of Pharmacology and Experimental Therapeutics 296:558-566, 2001.

2.1 For evaluating COX-2 activity, human blood was collected from volunteers, heparin is added (19 U/ml) and aliquots of 500 µl were incubated with LPS (100µg/ml) and with 2 µl of solutions (DMSO 1%) of the precursor compounds at different concentrations using 3-fold serial dilutions (1:10, 1:100, 1:1000 and 1:10000) of the highest tested concentration or with 2 µl vehicle (DMSO), for 24 h at 37°C. COX-2 activity in the samples has been determined in the plasma after deproteinization as PGE2 concentration using radioimmunoassay (Amersham, Oakville, Ontario, Canada).

2.2 For the evaluation of COX-1 activity, a 500 µl aliquot human blood was mixed with 2 µl of solutions (DMSO 1%) of the precursor compounds at different concentrations using 3-fold serial dilutions (1:10, 1:100, 1:1000 and 1:10000) of the highest tested concentration or with 2 µl vehicle (DMSO) and the blood was allowed to clot for 1 h at 37°C.

COX-1 activity in the samples was determined in the plasma after deproteinization as TXB₂ concentration using enzyme immunoassay (Cayman Chemicals, Ann Arbor, MI).

Test 2 is met by those precursor compounds having a COX-1 inhibiting activity / COX-2 inhibiting activity ratio, expressed as IC₅₀, greater than or equal 5.

The precursors that can be employed for the preparation of the compounds object of the present invention are described in the following patents or patent applications:

WO 91/ 19708, WO 94/13635, WO 94/15932, WO 94/20480, WO 94/26731, WO 94/27980, WO 95/00501, WO 95/11883, WO 95/15315, WO 95/15316, WO 95/15317, WO 95/15318, WO 95/18799, WO 95/21817, WO 95/30652, WO 95/30656, WO 96/03392, WO 96/03385, WO 96/03387, WO 96/03388, WO 96/06840, WO 96/09293, WO 96/09304, WO 96/10021, WO 96/13483, WO 96/16934, WO 96/19462, WO 96/19463, WO 96/19469, WO 96/21667, WO 96/23786, WO 96/24584, WO 96/24585, WO 96/25405, WO 96/31509, WO 96/36617, WO 96/36623, WO 96/37467, WO 96/37468, WO 96/37469, WO 96/38418, WO 96/38442, WO 96/41626, WO 96/41645, WO 97/03953, WO 97/11704, WO 97/13755, WO 97/13767, WO 97/14691, WO 97/16435, WO 97/25045, WO 97/27181, WO 97/28120, WO 97/28121, WO 97/29776, WO 97/34882, WO 97/36863, WO 97/37984, WO 97/38986, WO 97/40012, WO 97/41100, WO 97/44027, WO 97/44028, WO 97/45420, WO 98/00416, WO 98/03484, WO 98/04527, WO 98/05639, WO 98/06708, WO 98/07714, WO 98/11080, WO 98/14205, WO 98/21195, WO 98/22442, WO 98/32732, WO 98/33769, WO 98/39330, WO 98/41511, WO 98/41516, WO 98/43966, WO 98/43649, WO 98/46594, WO

98/47509, WO 98/47871, WO 98/47890, WO 98/50033, WO 98/50075, WO 98/52937,
WO 98/57924, WO 99/05104, WO 99/10331, WO 99/10332, WO 99/11605, WO
99/12930, WO 99/13799, WO 99/14194, WO 99/14195, WO 99/15205, WO 99/15503,
WO 99/15513, WO 99/15505, WO 99/18960, WO 99/20110, WO 97/27181, WO
5 97/28120, WO 97/28121, WO 97/29776, WO 97/34882, WO 97/36863, WO 97/37984,
WO 97/38986, WO 97/40012, WO 97/41100, WO 97/44027, WO 97/44028, WO
97/45420, WO 98/00416, WO 98/03484, WO 98/04527, WO 98/05639, WO 98/06708,
WO 98/07714, WO 98/11080, WO 98/14205, WO 98/21195, WO 98/22442, WO
98/32732, WO 98/33769, WO 98/39330, WO 98/41511, WO 98/41516, WO 98/43966,
10 WO 98/43649, WO 98/46594, WO 98/47509, WO 98/47871, WO 98/47890, WO
98/50033, WO 98/50075, WO 98/52937, WO 98/57924, WO 99/05104, WO 99/10331,
WO 99/10332, WO 99/11605, WO 99/12930, WO 99/13799, WO 99/14194, WO
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WO 99/20110, WO 99/20589, WO 99/21585, WO 99/22720, WO 99/23087, WO
15 99/25695, WO 99/33796, WO 99/35130, WO 99/41224, WO 99/45913, WO 99/55830,
WO 99/59634, WO 99/59635, WO 99/61016, WO 99/61436, WO 99/62884, WO
99/64415, WO 00/00200, WO 00/01380, WO 00/08024, WO 00/10993, WO 00/13685,
WO 00/23433, WO 00/24719, WO 00/25779, WO 00/26216, WO 00/27382, WO
00/29022, WO 00/29023, WO 00/37107, WO 00/38730, WO 00/38786, WO 00/40087.
20 WO 00/48583, WO 00/51685, WO 00/52008, WO 00/53149, WO 00/68215, WO
01/70704, WO 01/15138, WO 01/68633, EP 0087629, EP 0418845, EP 0554829, EP
0745596, EP 0788476, EP 0826676, EP 0863134, EP 0882016, EP 0927555, EP
0937722, EP 1006114, US 3,840,597, US 5,134,142, US 5,344,991, US 5,380,738, US
5,393,790, US 5,399,357, US 5,434,178, US 5,409,944, US 5,436,265, US 5,466,823,
25 US 5,474,995, US 5,475,021, US 4,486,534, US 5,504,215, US 5,508,426, US
5,510,368, US 5,510,496, US 5,516,907, US 5,521,207, US 5,521,213, US 5,536,752,
US 5,550,142, US 5,552,422, US 5,563,165, US 5,580,985, US 5,585,504, US
5,596,008, US 5,604,253, US 5,604,260, US 5,616,601, US 5,620,999, US 5,633,272,
US 5,639,780, US 5,643,933, US 5,668,161, US 5,677,318, US 5,686,170, US
30 5,686,460, US 5,691,374, US 5,696,143, US 5,698,584, US 5,700,816, US 5,710,140,
US 5,719,163, US 5,733,909, US 5,753,688, US 5,756,530, US 5,760,068, US
5,783,597, US 5,789,413, US 5,807,873, US 5,817,700, US 5,840,746, US 5,840,924,
US 5,849,943, US 5,859,257, US 5,861,419, US 5,883,267, US 5,908,852, US
5,908,858, US 5,925,631, US 5,935,990, US 5,945,539, US 5,972,986, US 5,981,576,
35 US 5,985,902, US 5,990,148, US 5,994,379, US 5,994,381, US 6,001,843, US

6,002,014, US 6,020,343, US 6,025,353, US 6,028,072, US 6,046,191, US 6,071,936, US 6,071,954, US 6,077,869, US 6,080,876, US 6,083,969, US 6,136,839, US 5,681,842, US 5,776,967, US 5,824,699, US 5,883,267, US 5,905,089, US 5,908,858, US 5,945,538, US 5,980,905, US 5,994,381, US 6,004,948, US 2002/0058690 and JP

5 2001139575.

Examples of preferred COX-2 selective inhibitors of formula M-TH or M-TOH are listed here below:

4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide (Valdecoxib), 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (Celecoxib), 4-
10 (4-cyclohexyl-2-methyloxazol-5-yl)-2-fluoro-benzenesulfonamide (Tilmacoxib), N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]-methanesulfonamide (L-745337), N-(4-nitro-2-fenoxyphenyl)methanesulfonanilide, N-(4-nitro-2-cyclooxyloxy-phenyl)methanesulfonanilide, 2-[(2-chloro-6-fluorophenyl)-amino]-5-methylbenzeneacetic acid (COX189), 2-[(2-chloro-6-fluorophenyl)-amino]-4-
15 methylbenzeneacetic acid.

Preferred drugs of formula (I) according to the invention are:
N-(6-(2,4-difluorophenyl)thio-2,3-dihydro-1-oxo-1-inden-5-yl)-N-(4-nitrooxybutyroyloxymethyl)methanesulfonamide, N-(6-(2,4-difluoro-phenyl)thio)-2,3-dihydro-1-oxo-1-inden-5-yl)-N-(3-nitrooxymethyl)-
20 benzoyloxymethyl)methanesulfonamide, (Z)-2-(4-methylsulfonyl)phenyl)-3-phenyl-2-buten-1,4-diol-1-((4-nitrooxymethyl)benzoate), N-(4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenylsulfonyl)-4-nitrooxybutanamide, N-(3-nitrooxymethyl)benzoyl-oxymethyl-N-(2-phenoxy-4-nitrophenyl)methanesulfonamide.

As a few compounds of formula (I) possess one or more asymmetrical carbon atoms, they can exist as optically pure enantiomers, pure diastereomers, enantiomer mixtures, diastereomers mixtures, enantiomer racemic mixtures, racemates or racemate mixtures. The object of the invention are also all these stereoisomers as well mixtures thereof. Compounds of the invention comprise a carbon-carbon double bond may exist as E or Z geometrical isomers, it is to be understood that the present 30 invention includes all these isomers as well mixtures thereof.

As mentioned above, object of the present invention are also pharmaceutical compositions containing at least a compound of the present invention of formula (I) together with non toxic adjuvants and/or vehicles usually employed in the pharmaceutical field.

The daily dose of active ingredient that should be administered can be a single dose or it can be an effective amount divided into several smaller doses that are to be administered throughout the day. Usually, total daily dose may be in amounts from 1 to 2000 mg, preferably from 10 to 1000 mg, in particular from 50 to 500 mg. The dosage regimen and administration frequency for treating the mentioned diseases with the compound of the invention and/or with the pharmaceutical compositions of the present invention will be selected in accordance with a variety of factors, including for example age, body weight, sex and medical condition of the patient as well as severity of the disease, route of administration pharmacological considerations and eventual concomitant therapy with other drugs. In some instances, dosage levels below or above the aforesaid range and/or more frequent may be adequate, and this logically will be within the judgment of the physician and will depend on the disease state.

The compounds of the invention may be administered orally, parenterally, rectally or topically, by inhalation or aerosol, in formulations eventually containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or ionophoresis devices. The term "parenteral" as used herein, includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

Injectable preparations, for example sterile injectable aqueous or oleaginous suspensions may be formulated according to known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents are water, Ringer's solution and isotonic sodium chloride. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono or diglycerides, in addition fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the active ingredient with a suitable non-irritating excipient, such as cocoa butter and polyethylene glycols.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, granules and gels. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert

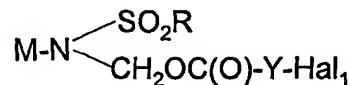
diluents, e.g. lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring and the like.

The synthesis methods of the precursor drugs are reported in the publications mentioned above. The precursor compounds of B described above are compounds available on the market or they can be obtained according to methods well-known in the art and described for example in "The Merck Index" 13th Ed. (2001). The precursors of Y having the formula (IA), wherein the free valence of oxygen is saturated with H and the free valence of carbon is saturated with a carboxylic, hydroxy or amine group, are products available on the market or they can be prepared according to methods well known in the art.

Generally, the nitrooxyderivatives of the present invention may be synthetized using methods known from literature or as reported in the following patents or patent applications in the name of Applicant: EP 722434, EP 759899, WO 00/51988, WO 00/61537, WO 00/61541.

A) The compounds of formula (I) as above defined wherein T is $-N(SO_2R)$, $b_0 = 0$, $c_0 = 1$, $T_c = -(CH_2)_{n_6}O(CO)-$, wherein R, Y, are as defined above and $n_6 = 1$ are obtained by reacting a compound of formula (II)

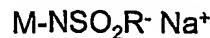


(II)

wherein M, R, are as defined above Y has one of meanings mentioned above wherein the oxygen terminal atom is absent and replaced by an halogen atom Hal_1 in formula (II), and Hal_1 is an halogen atom, preferably Br or Cl, with AgNO_3 .

The reaction is carried out in a suitable organic solvent, such as acetonitrile or THF at a temperature of from 0° to 80°C.

The compounds of formula (II) as above defined are obtained by reacting a compound of formula (III)



(III)

wherein M, R, are as defined above with a compound of formula (IV)



(IV)

wherein Hal is an Halogen atom, Hal and Hal₁ my have the same or a different meaning, Y has one of meanings mentioned above wherein the oxygen terminal atom is absent and replaced by an halogen atom Hal₁ in formula (IV).

The reaction is carried out in a suitable solvent, such as dry THF at a temperature of from 0° to 80°.

10 The compounds of formula (III) are commercially available compounds or may be obtained by salifying the corresponding secondary sulfonamide groups by well known reactions or can be obtained by well known reactions described in the patents or patent applications reported above.

The compounds of formula (IV) are commercially available compounds or may be obtained from known compounds by known reactions.

15 B) The compounds of formula (I) as above defined wherein T = -SO₂NH, b0 = 0, c0 = 1, T_c = CO wherein M, Y, are as defined above are obtained by reacting a compound of formula (V)



(V)

20 wherein M is as defined above, Y has one of meanings mentioned above wherein the oxygen terminal atom is absent and replaced by an halogen atom Hal₁ in formula (V), and Hal₁ is an halogen atom, preferably Br or Cl , with AgNO₃.

The reaction is carried out in a suitable organic solvent, such as acetonitrile or THF at a temperature of from 0° to 80°C.

25 The compounds of formula (V) as above defined are obtained by reacting a compound of formula (VI)



wherein M is as defined above with a compound of formula (VII) or the corresponding anhydride of formula (VIII)

30 Hal-C(O)-Y- Hal₁ (VII) or (Hal₁-Y-CO)₂ (VIII)

wherein Hal₁ is as defined above, Hal is an Halogen atom, Hal and Hal₁ my have the same or a different meaning, Y has one of meanings mentioned above wherein the oxygen terminal atom is absent and replaced by an halogen atom Hal₁ in formulas (VI) and (VII).

The reaction is carried out in a suitable solvent, such as for example THF or DMF at a temperature of from 0° to 80°.

The compounds of formula (VI) are commercially available compounds or can be obtained by well known reactions described in the patents or patent applications 5 reported above.

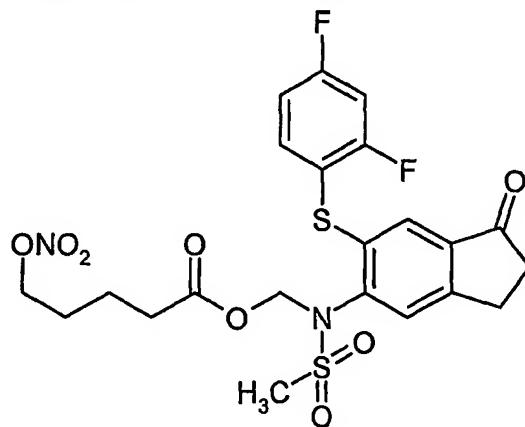
The compounds of formula (VII) and (VIII) are commercially available compounds or may be obtained from known compounds by known reactions.

The invention will now be described in greater detail by reference to the following non-limiting examples.

10

Example 1

N-[6-(2,4-Difluorophenyl)thio]-2,3-dihydro-1-oxo-1-inden-5-yl]-N-[4-(nitrooxy)butyroyloxymethyl]-methanesulfonamide



15 1.A) N-[6-(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1-inden-5-yl]-N-[4-(chloro)butyroyloxymethyl]methanesulfonamide (1A)

A solution of chloromethyl (4-chloro)butyrate (1 g, 5.40 mmol) in anhydrous tetrahydrofuran (5 ml) was slowly added dropwise in a suspension of N-[6-(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1-inden-5-yl]-methanesulfonamide sodium salt

20 (2.04 g, 5.40 mmol) in anhydrous tetrahydrofuran (25 ml). The reaction was allowed to stand under stirring overnight at room temperature. The solvent was evaporated under vacuum, the residue was treated with methylene chloride (40 ml) and the solution thus obtained was washed with a 5% sodium bicarbonate solution and then with water. The organic phase was dried on sodium sulphate. The crude product was purified by chromatography on a silica gel column with n-hexane/ ethyl acetate 8/2 as eluent to give 1.12 g of the desired product.

1.B) N-[6-(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1-inden-5-yl]-N-[4-(nitrooxy)butyroyloxymethyl]- methanesulfonamide

A solution of product 1A (1 g, 1.98 mmol) in acetonitrile (20 ml) was added with silver nitrate (0.67 g, 3.96 mmol). The solution was heated at 80°C for 15 hours in absence 5 of light. The silver salts were filtered off and solvent was evaporated under vacuum. The crude product thus obtained was purified by chromatography on a silica gel column with n-hexane/ethyl acetate 8/2 as eluent to give 503 mg of the title product.

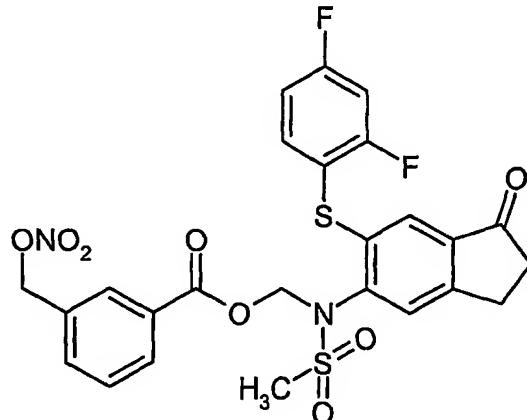
Elemental Analysis

Calculated: C 48,64%; H 4,27%; F 7,32%; S 12,37%

10 Found: C 48,57%; H 4,03%; F 7,31%; S 12,33%

Example 2

N-[6-(2,4-Difluorophenyl)thio]-2,3-dihydro-1-oxo-1-inden-5-yl]-N-[3-(nitrooxymethyl)benzoyloxymethyl] methanesulfonamide



15

2.A) N-[6-(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1-inden-5-yl]-N-[3-(chloromethyl)benzoyloxymethyl]methanesulfonamide (2A)

A solution of chloromethyl (3-chloromethyl)benzoate (1.5 g, 6.80 mmol) in anhydrous tetrahydrofuran (7 ml) was slowly added dropwise in a suspension of N-[6-(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1-inden-5-yl]methanesulfonamide sodium salt 20 (2.57 g, 6.80 mmol) in anhydrous tetrahydrofuran (45 ml). The reaction was allowed to stand under stirring overnight at room temperature. The solvent was evaporated under vacuum, the residue was treated with methylene chloride (60 ml) and the solution thus obtained was washed with a solution of 5% sodium bicarbonate and then with water. 25 The organic phase was dried on sodium sulphate. The crude product thus obtained was purified by chromatography on silica gel column with n-hexane/ethyl acetate 8/2 as eluent to give 1.31 g of the desired product.

2.B) N-[6-(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1-inden-5-yl]-N-[3-(nitrooxymethyl)benzoyloxymethyl]-methanesulfonamide

A solution of product 2A (1 g, 1.86 mmol) in acetonitrile (20 ml) was added with silver nitrate (0.47 g, 2.78 mmol). The solution was heated at 80°C for 15 hours in absence of light. The silver salts were filtered off and the solvent was evaporated under vacuum. The crude product thus obtained was purified by chromatography on a silica gel column with n-hexane/ethyl acetate as eluent 8/2 to give 623 mg of title compound.

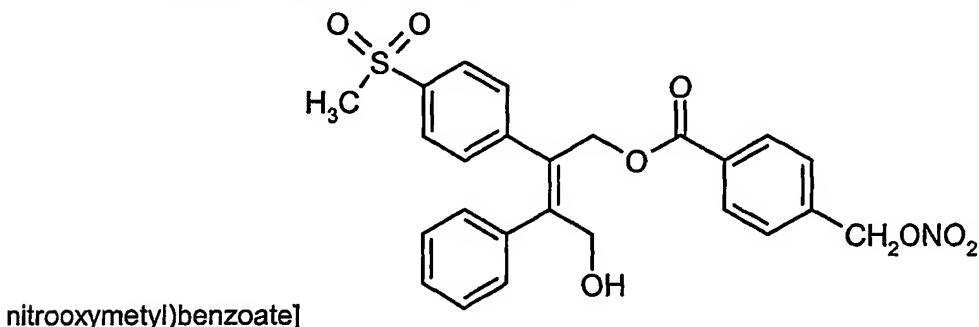
Elemental analysis

Calculated: C 53,19%; H 3,56%; F 6,73%; S 11,60%

10 Found: C 53,27%; H 3,43%; F 6,79%; S 11,5%

Example 3

(Z)-2-(4-Methylsulphonylphenyl)-3-fenyl-2-buten-1,4-diol-1-[(4-



nitrooxymethyl)benzoate]

15 3.A) (Z)-2-(4-methylsulphonylphenyl)-3-phenyl-2-buten-1,4-diol

A solution of 1M DIBAL in toluene (185 ml) was slowly added into a solution of 3-[phenyl-4-(4-methylsulphonyl)phenyl]-2-(5H)-furanone (18.1 g, 57.1 mmol) in tetrahydrofuran (750 ml).

The solution was allowed to stand under stirring at 0°C for 90 minutes, then overnight at room temperature. Into the reaction mixture cooled at 0°C a 1M solution of sodium potassium tartrate was added dropwise. The solution was extracted with ethyl acetate and the organic phase was washed with water and dried with sodium sulphate to give 15 g of the desired compound.

3.B) (Z)-2-(4-methylsulphonylphenyl)-3-phenyl-2-buten-1,4-diol-1-[(4-

25 chloromethyl)benzoate] (3B)

A solution of (Z)-2-(4-methylsulphonylphenyl)-3-phenyl-2-buten-1,4-diol (15 g, 46.7 mmol), triethylamine (13.3 ml, 95.7 mmol) and 4-dimethylaminopyridine (0.76 g, 6.26 mmol) in methylene chloride (30ml), cooled at 0°C, was slowly added with a solution of 4-chloromethyl benzoyl chloride (8.8 g, 46.7 mmol) in methylene chloride (30 ml). The

reaction mixture was allowed to stand under stirring for 30 min and then acidified with 1N HCl (100 ml). The separated organic phase was dried with sodium sulphate and concentrated under vacuum. The crude compound thus obtained was purified by chromatography on a silica gel column with n-hexane/ethyl acetate 8/2 as eluent to give 4.3 g of the title compound.

5 3.C) (Z)-2-(4-methylsulphonylphenyl)-3-phenyl-2-buten-1,4-diol-1-[(4-nitrooxymethyl)benzoate]

To a solution of product 3B (3 g, 6.38 mmol) in acetonitrile (60 ml) silver nitrate was added (1.07 g, 6.38 mmol). The solution was heated at 50°C for 8 ore in absence of light. The silver salts were filtered off and the solvent was evaporated under vacuum. The crude product thus obtained was purified by chromatography on a silica gel column with n-hexane/ethyl acetate 8/2 as eluent to give 1.3 g of the title compound.

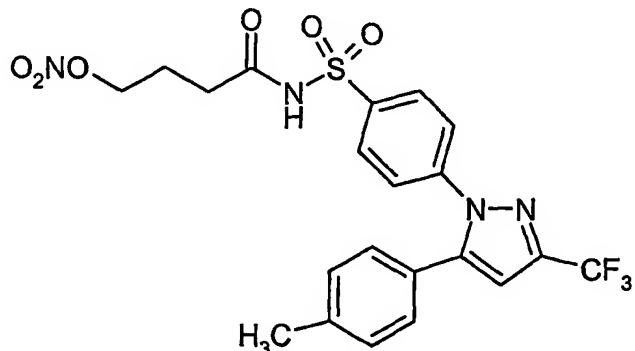
Elemental analysis

Calculated: C 60,36%; H 4,65%; S 6,43%

15 Found: C 60,40%; H 4,63%; S 6,33%

Example 4

Synthesis of N-[4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenylsulfonyl]-4-nitrooxy-butanamide



20

4.A) N-[4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenylsulfonyl]-4-chlorobutanamide(4A).

At a solution of N-[4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenylsulfonyl]benzenesulfonamide (1 g, 2.262 mmol) in pyridine (50 ml) cooled at 0°C, 4-chlorobutyrylchloride was added dropwise (0.294 ml), the solution was maintained under stirring for 10 minutes at 0°C, the temperature was then raised to room temperature and the solution was maintained under stirring for 2 hours. Then HCl was added (50 ml, 0.1 N) and the mixture was extracted with CH₂Cl₂. The combined

organic phases were washed with water, dried and the solvent was evaporated at reduced pressure. The crude compound was purified by chromatography on a silica gel column with n-heptane/ethyl acetate 8/2 as eluent to give 0.400 mg of product 4A.

4.B) N-[4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenylsulfonyl]-4-nitrooxybutanamide.

To a solution of product 4A (0.380 g, 0.78 mmol) in acetonitrile (5 ml) silver nitrate was added (0.265 g, 1.56 mmol) and the solution was heated for 8 hours at 50°C in absence of light. The silver salts were filtered off and the solvent was evaporated at reduced pressure. The crude product thus obtained was purified by chromatography on a silica gel column with n-hexane/ethyl acetate 8/2 as eluent to give 0.4 g of the title compound.

Elemental analysis:

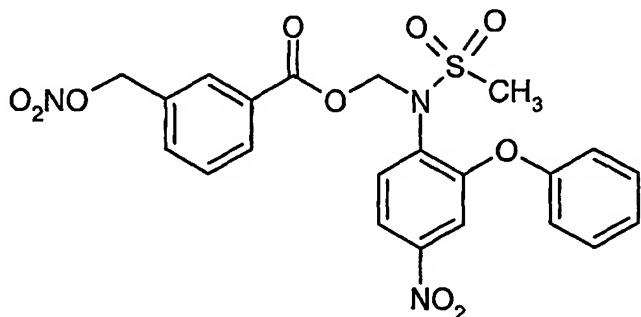
Calculated: C 49,22%; H 3,74%; S 6,26% F 11,12%

Found: C 49,26%; H 3,77%; S 6,28% F 11,09%

15

Example 5

Synthesis of N-[(3-nitrooxymethyl)benzoyloxymethyl]-N-(2-phenoxy-4-nitrophenyl)methanesulfonamide



20

5.A) N-[(3-chloromethyl)benzoyloxymethyl]-N-(2-phenoxy-4-nitrophenyl)methanesulfonamide (5A)

A solution of chloromethyl 3-chloromethylbenzoate (1.5 g, 6.80 mmol) in anhydrous tetrahydrofuran (7 ml) was slowly added dropwise in a suspension of N-(2-phenoxy-4-nitrophenyl)methanesulfonamide sodium salt (2.25 g, 6.80 mmol) in anhydrous tetrahydrofuran (45 ml). The reaction was allowed to stand overnight under stirring at room temperature. The solvent was evaporated at reduced pressure, the residue was dissolved in methylene chloride (60 ml) and the solution thus obtained was washed with a 5% sodium bicarbonate solution and then with water. The organic phase was

dried on sodium sulphate. The crude product thus obtained was purified by chromatography on a silica gel column with n-hexane/ethyl ether 7/3 as eluent to give 0.830 g of product 5A.

5.B) . . . N-[6-(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1-inden-5-yl]-N-[3-(nitrooxymethyl)benzoyloxymethyl]methanesulfonamide

To a solution of product 5A (0.8 g 1.63 mmol) in acetonitrile (20 ml) Silver nitrate was added (0.55 g, 0.32 mmol). The solution was heated at 80°C for 15 hours in absence of light. The silver salts were filtered off and the solvent was evaporated under vacuum. The crude product thus obtained was purified by chromatography on a silica gel column with n-hexane/diethyl ether 8/2 to give 0.330 g of the desired product.

¹H NMR(CDCl₃) ppm: 3,26 (3H,s); 5,98 (2H, s); 5,5 (2H, s); 6,98-8,01 (17H, m).

Example F1

Comparison of gastric tolerability and blood pressure effect of the compounds of the invention vs precursor compound.

The experiment was carried out according to the method described by M. N. Muscarà et al. Br. J. Pharmacol. 133, 1314, 2001, and employing groups of 10 rats weighing each 200-250 g.

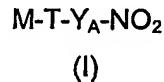
The compounds, suspended in 1% carboxymethylcellulose, were administered orally for two weeks at a daily dose of 10 mg/kg body weight.

Hypertension was induced by addition of L-NAME (N-omega-nitro-L-arginine methylester) to the drinking water at a concentration of 400 mg/liter. At the end of the treatment, the blood pressure was determined by introduction of a cannula into femoral artery and measurement with polygraphic transducer, 16 hours after the last administration. The animals were then sacrificed and the eventual gastric damage was revealed.

The results show that the product object of the invention described in example 4, N-[4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenylsulphonyl]-4-nitrooxybutanamide, is well tolerated without no increase of the blood pressure. At contrary, the reference COX-2 inhibitor celecoxib causes a gastric damage into 80% of the treated animals and an increase of the blood pressure on an average of 15 mmHg.

CLAIMS

1. A compound of formula (I) or a salt thereof which are able to release COX-2 inhibitors and NO (nitrogen oxide) under conditions and according to the parameters
 5 set up in test 1 mentioned in the description



wherein:

M-T is the residue of a COX-2 selective inhibitor, in which T = -SO₂NH-, -SO₂NR-,
 10 -CO-, -O-, -S-, -NH-, -N(SO₂R)-, R being alkyl with 1-10 carbon atoms, wherein the
 COX-2 selective inhibitor, M-TH or M-TOH, has to meet test 2 mentioned in the
 description,

Y_A = -(B)_{b0}-(C)_{c0}- wherein:

b0 e c0 are the integers 1 or 0, with the proviso that b0 and c0 cannot be
 15 simultaneously 0,

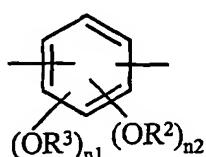
B = -T_B-X₂-T_{B1}-, in which:

T_B = CO or X, wherein X = O, S, NH, NR, and R is as defined above, T_B is CO when T
 is -SO₂NH-, -SO₂NR-, -O-, -S-, -NH-, -N(SO₂R)-, T_B is X when T is -CO-;

T_{B1} = CO or X, in which X is as defined above;

20 X₂ is a divalent radical and is selected from the following compounds:

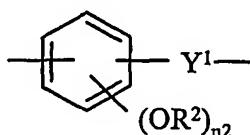
a)



wherein:

n1 and n2 are integers 0 or 1; R² and R³ are independently selected from H or CH₃;

25 b)

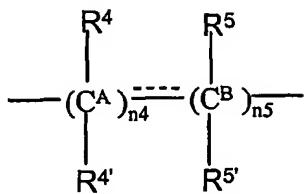


wherein:

n2 and R² are as above defined;

Y¹ is -CH₂-CH₂- or -CH=CH-(CH₂)_{n2'}- wherein n2' is an integer 0 or 1;

c)



wherein:

5 n4 is an integer from 1 to 20 and n5 is an integer from 0 to 20, R⁴, R^{4'}, R⁵ and R^{5'} are independently selected from H, CH₃, OH, NH₂, NHCOCH₃, COOH; when the bond between the C^A and C^B carbons is a double bond R⁴ and R⁵ or R^{4'} and R^{5'} are absent; C is the bivalent radical -T_C-Y-, wherein:

T_C = CO, X wherein X is as defined above, or -(CH₂)_{n6}OC(O)- wherein n6 is an integer from 1 to 20;

10 Y is a bivalent radical having the following meanings:

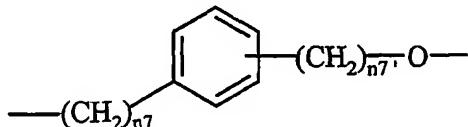
d) -R¹O-, in which R¹ is:

- straight or branched C₁-C₂₀-alkylene optionally containing one or more heteroatoms selected from oxygen, nitrogen, sulphur, or one or more groups -O(CO)-, -NH(CO)-, -S(CO)-, optionally substituted with one or more of the following groups -OH, -SH, -NH₂,

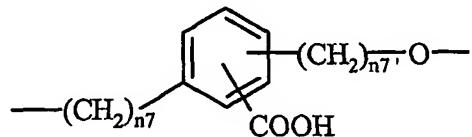
15 -NHCOR⁶, in which R⁶ is straight or branched C₁-C₁₀-alkyl;

- cycloalkylene containing from 5 to 7 carbon atoms into cycloalkylene ring, wherein one or more carbon atoms can be replaced by heteroatoms selected from nitrogen, oxygen or sulphur, and the ring can be substituted with side chains R⁶, R⁶ being as defined above;

20 e)

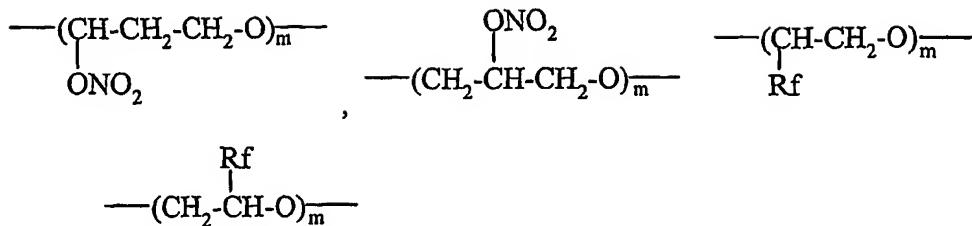


f)



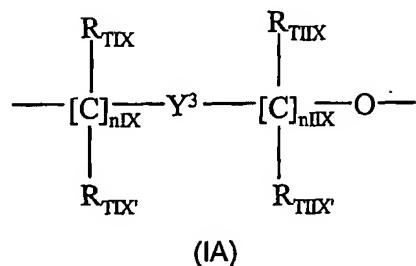
wherein n7 is an integer from 0 to 20, and n7' is an integer from 1 to 20;

g)



wherein m is an integer from 1 to 6, Rf is a hydrogen atom or CH₃;

5 h)



wherein:

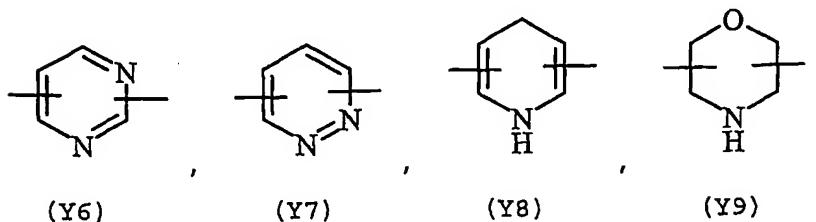
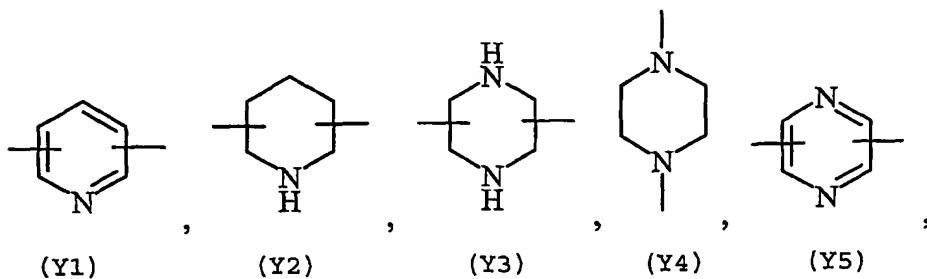
nIX is an integer from 0 to 10;

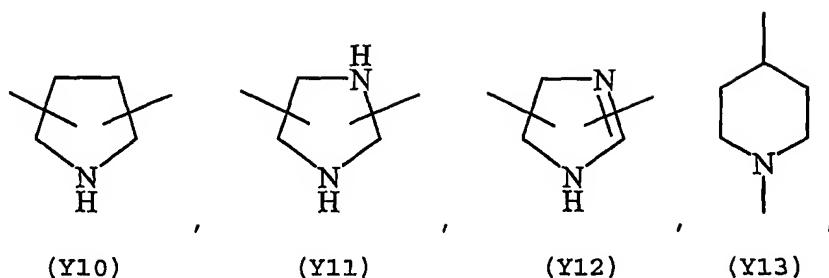
10 nIIIX is an integer from 1 to 10;

R_{nIX}, R_{nIX'}, R_{nlIX}, R_{nlIX'}, are the same or different, and are H or straight or branched C₁-C₄-alkyl;

Y³ is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulphur, and

15 selected from





with the proviso that:

5 when $b_0 = 0$, $c_0 = 1$ and $T = -SO_2NH-$, $-SO_2NR-$, $-O-$, $-S-$, $-NH-$, $-N(SO_2R)-$
wherein R is as defined above, then $T_C = (CO)$ or $-(CH_2)_{n_6}O(CO)-$;

when $b_0 = 0$, $c_0 = 1$ and $T = CO$ then $T_C = X$ wherein X is as defined above;

when $b_0 = 1$ and $T = -SO_2NH-$, $-SO_2NR-$, $-O-$, $-S-$, $-NH-$, $-N(SO_2R)-$ wherein R is
as defined above, then $T_B = CO$;

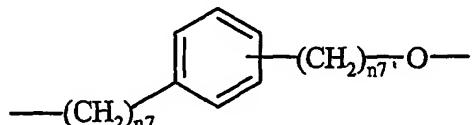
when $b_0 = 1$ and $T = CO$ then $T_B = X$ wherein X is as defined above;

10 when $b_0 = 1$, $c_0 = 1$ and $T_{B1} = CO$ then $T_C = X$ wherein X is as above defined;

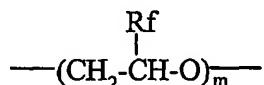
when $b_0 = 1$, $c_0 = 1$ and $T_{B1} = X$, wherein X is as above defined, then $T_C = (CO)$;

when $b_0 = 1$, $c_0 = 0$ the T_{B1} has only the meaning of $-O-$;

15 2. A compound of formula (I) according to claim 1 wherein $b_0 = 0$, $c_0 = 1$, T and T_c are as defined in claim 1, Y is a straight C₁-C₆ alkylene or



wherein n7 is 0 or 1, and n7' is 1 or 2, or



20 wherein m is 2, Rf is hydrogen.

3. A compound of formula (I) according to claim 2 wherein $b_0 = 0$, $c_0 = 1$, $T = -N(SO_2R)-$, $T_C = CO$ or $-(CH_2)_{n_6}O(CO)-$ wherein $n_6 = 1$ and $R = CH_3$.

25 4. A compound of formula (I) according to claim 2 wherein $b_0 = 0$, $c_0 = 1$, $T = -SO_2NH-$
and $T_c = CO$ or $-(CH_2)_{n_6}O(CO)-$ wherein $n_6 = 1$.

5. A compound of formula (I) or a salt thereof according to claims 1 to 4 wherein M-T is
e residue of a COX-2 selective inhibitor of formula M-TH or M-TOH selected from the
group consisting of 4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide, 4-[5-(4-
methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, 4-(4-cyclohexyl-
5 2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide, N-[6-[(2,4-difluorophenyl)thio]-2,3-
dihydro-1-oxo-1H-inden-5-yl]-methanesulfonamide, N-(4-nitro-2-phenoxyphenyl)
methanesulfonanilide, N-(4-nitro-2-cyclohexyloxyphenyl)methane sulfonanilide, 2-[(2-
chloro-6-fluorophenyl)amino]-5-methylbenzeneacetic acid, 2-[(2-chloro-6-fluorophenyl)-
amino]-4-methylbenzeneacetic acid.

10 6. A compound according to claim 3, that is N-[6-(2,4-difluorophenylthio)-2,3-dihydro-
1-oxo-1-inden-5-yl]-N-[(4-nitrooxy)butyroyloxymethyl] methanesulfonamide.

15 7. A compound according to claim 3, that is N-[6-(2,4-difluorophenylthio)-2,3-dihydro-
1-oxo-1-inden-5-yl]-N-[3-(nitrooxymethyl)benzoyloxymethyl] methanesulfonamide.

8. A compound according to claim 3, that is (Z)-2-(4-methylsulphonylphenyl)-3-phenyl-
2-buten-1,4-diol-1-[(4-nitrooxymethyl)-benzoate]).

20 9. A compound according to claim 4, that is N-[4-[5-(4-methylphenyl)-3-
(trifluoromethyl)-1H-pyrazol-1-yl]phenylsulfonyl]-4-nitrooxybutanamide.

10. A compound according to claim 3, that is N-(3-nitrooxymethyl)benzoyloxymethyl-N-
(2-phenoxy-4-nitrophenyl)methane-sulfonamide.

25 11. A compound of formula (I) or a salt thereof according to claims 1-10 as therapeutic
agent.

30 12. Use of a compound of formula (I) or a salt thereof according to claims 1-10, for
preparing a drug that can be employed in the treatment or prophylaxis of inflammatory
disorders, pain and fever.

35 13. Use according to claim 12, characterized in that the inflammatory disorders are
selected from the group consisting of, but not limited to, arthritis, reumatoid arthritis,
osteoarthritis, dysmenorrhea, allergic rhinitis, sinusitis, chronic obstructive pulmonary

diseases, dermatitis, psoriasis, cystic fibrosis, multiples sclerosis, vasculitis and organ transplant rejection.

14. Use of a compound of general formula (I) or a salt thereof according to claims 1-10,
5 for preparing a drug that can be employed in the treatment or prophylaxis of
cardiovascular diseases.

15. Use according to claim 14, characterized in that the cardiovascular diseases are
selected from the group consisting of, but not limited to, atherosclerosis, restenosis,
10 coronary artery disease, angina, diabetes mellitus, diabetic nephropathy, diabetic
retinopathy, stroke and myocardic infarct.

16. Use of a compound of general formula (I) or a salt thereof according to claim 1-10,
for preparing a drug that can be employed in the treatment or prophylaxis of
15 gastrointestinal disorders.

17. Use according to claim 16, characterized in that the gastrointestinal disorders are
selected from the group consisting of, but not limited to, inflammatory intestinal
disorders, Crohn's disease, gastritis, ulcerative colitis, peptic ulcer, haemorrhagic ulcer,
20 gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison's syndrome, bacterial
infections, hypersecretory states associated with systemic mastocytosis or basophilic
leukaemia and hyperhystaminemia.

18. Use of a compound of general formula (I) or a salt thereof according to claim 1-10,
25 for preparing a drug that can be employed in the treatment or prophylaxis of tumors
and Alzheimer's disease.

19. Use of a compound of general formula (I) or a salt thereof according to claim 1-10,
for preparing a drug that can be employed for treating or preventing disorders resulting
30 from elevated levels of COX-2.

20. Use according to claim 19, characterized in that the disorders resulting from
elevated levels of COX-2 are selected from the group consisting of, but not limited to,
angiogenesis, arthritis, asthma, bronchitis, menstrual cramps, tendinitis, bursitis,
35 neoplasia, ophthalmic diseases, pulmonary inflammations, central nervous system

disorders, allergic rhinitis, atherosclerosis, endothelial disorders, organs and tissues preservation, inhibition and/or prevention of platelets aggregation.

21. A pharmaceutical composition comprising a pharmaceutically acceptable carrier
5 and a pharmaceutically effective amount of a compound of general formula (I) or a salt thereof according to claim 1-10.
22. A composition according to claim 21 in a suitable form for the oral, parenteral, rectal, topic and transdermic administration, by inhalation spray or aerosol or
10 iontophoresis devices.
23. Liquid or solid pharmaceutical composition for oral, parenteral, rectal, topic and transdermic administration or inhalation in the form of tablets, capsules and pills eventually con enteric coating, powders, granules, gels, emulsions, solutions,
15 suspensions, syrups, elixir, injectable forms, suppositories, in transdermal patches or liposomes, containing a compound of formula (I) according to claim 1-10 or a salt thereof and a pharmaceutically acceptable carrier.

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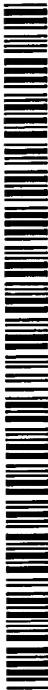
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WO 2004/000781 A3

(54) Title: NITROOXYDERIVATIVES OF CYCLOOXYGENASE-2 INHIBITORS

(57) Abstract: New compounds able to release COX-2 inhibitors and NO having formula (I):M-T-Y_A-NO₂ (I) for the treatment and/or prophylaxis of inflammatory processes.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 03/06502

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C323/49 C07C317/22 C07D231/12 C07C311/08 A61K31/235 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 09948 A (NICOX SA) 12 March 1998 (1998-03-12) page 7, lines 1-15; pages 23-25, V Ac1-Ac5; page 31, line 8 - page 33, line 2; page 38, line 21 - page 42, line 22; page 45, line 6 - page 49, line 15 idem	1,2,5, 11,12, 14,15, 19-23
Y		1,2,5, 11-13, 20-23
Y	WO 96 25405 A (G.D. SEARLE & CO) 22 August 1996 (1996-08-22) cited in the application page 2, lines 4-8; example 1	1,2,5, 11-13, 20-23
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the International filing date but later than the priority date claimed

"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the International search

12 January 2004

Date of mailing of the International search report

23.01.2004

Name and mailing address of the ISA

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Van Amsterdam, L

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/06502

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 994 381 A (J. HARUTA ET AL) 30 November 1999 (1999-11-30) cited in the application example 2; column 34, line 65 - column 35, line 13 & WO 96 19463 A 27 June 1996 (1996-06-27). cited in the application & EP 0 826 676 A 4 March 1998 (1998-03-04) cited in the application & EP 0 745 596 A 4 December 1996 (1996-12-04) cited in the application & US 5 945 539 A 31 August 1999 (1999-08-31) cited in the application	1,2,5, 11-13, 20-23
A	WO 01 45703 A (NITROMED INC) 28 June 2001 (2001-06-28) page 1, lines 8-20; page 94, line 30 - page 104, line 4; examples 1, 2, 4-6, 8, 9, 18-20	1,11-23
Y	WO 02/30866 A (NICOX SA) 18 April 2002 (2002-04-18) example 10	1,2,5,8, 11-13, 16-23
Y	WO 96/13483 A (MERCK FROST CANADA INC) 9 May 1996 (1996-05-09) cited in the application page 8, line 4 - page 14, line 21; table II, compound 1 & EP 0 788 467 A 13 August 1997 (1997-08-13) cited in the application & US 5 849 943 A 15 December 1998 (1998-12-15) cited in the application	1,2,5,8, 11-13, 16-23
Y	WO 99/11605 A (NOVARTIS AG) 11 March 1999 (1999-03-11) cited in the application page 25, table 1, example 6; claims 1, 3-8	1,2,5, 11-13, 19-23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/06502

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claim 1 relates to an extremely large number of possible compounds. In fact, the claim contains so many options, variables and provisos that a lack of clarity (and conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claim impossible. The search has been guided by those parts of the application which do appear to be sufficiently clear (and concise), namely examples 1-5 and claims 2-10. The search has mainly related to compounds of formula I, wherein

M-T = is the residue of a COX-2 selective inhibitor as defined in claim 5

b0 = 0 and c0 = 1;

TC = as defined in claim 1;

Y = d) -R10-, in which R1 is straight or branched C1-C6 alkylene (cf. claim 1 vs. claim 2), e) as defined in claim 2 or g) as defined in claim 2.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/06502

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 9809948	A	12-03-1998	IT AU AU BR CA CN WO EP JP RU	MI961821 A1 729533 B2 4301097 A 9712008 A 2264081 A1 1234792 A 9809948 A2 0931065 A2 2000517332 T 2210563 C2	04-03-1998 01-02-2001 26-03-1998 24-08-1999 12-03-1998 10-11-1999 12-03-1998 28-07-1999 26-12-2000 20-08-2003
WO 9625405	A	22-08-1996	US AT AU AU BR CA CN CN CZ DE DE DK EP EP ES FI JP JP JP JP LU NO NZ PL PL PT RU WO US US ZA	5633272 A 223390 T 699593 B2 4867196 A 9607035 A 2212836 A1 1442139 A 1181075 A ,B 9702546 A3 69623444 D1 69623444 T2 809636 T3 1223167 A2 0809636 A1 2183935 T3 973292 A 3267300 B2 11503722 T 2002179656 A 91024 A9 973711 A 302586 A 321814 A1 185544 B1 809636 T 2200158 C2 9625405 A1 5859257 A 5985902 A 9601150 A	27-05-1997 15-09-2002 10-12-1998 04-09-1996 04-11-1997 22-08-1996 17-09-2003 06-05-1998 14-01-1998 10-10-2002 05-06-2003 06-01-2003 17-07-2002 03-12-1997 01-04-2003 10-10-1997 18-03-2002 30-03-1999 26-06-2002 04-08-2003 06-10-1997 30-08-1999 22-12-1997 30-05-2003 31-12-2002 10-03-2003 22-08-1996 12-01-1999 16-11-1999 12-02-1997
US 5994381	A	30-11-1999	JP JP AT AU AU BR CA CA CA CN CZ DE DE DK EP EP	2636819 B2 9052882 A 180253 T 695045 B2 4189796 A 9506815 A 2183645 A1 2208316 A1 2341921 A1 1146204 A 9602749 A3 69509753 D1 69509753 T2 745596 T3 0826676 A1 0745596 A1	30-07-1997 25-02-1997 15-06-1999 06-08-1998 10-07-1996 09-09-1997 27-06-1996 27-06-1996 27-06-1996 26-03-1997 11-12-1996 24-06-1999 02-12-1999 08-11-1999 04-03-1998 04-12-1996

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No	
PCT/EP 03/06502	

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
US 5994381	A		ES 2132751 T3 FI 963238 A GR 3030643 T3 HU 76541 A2 WO 9619462 A1 WO 9619463 A1 JP 3181190 B2 JP 8325249 A KR 201581 B1 NO 963450 A NZ 297105 A SK 117596 A3 TW 403742 B US 6002014 A US 6362209 B1 US 5945539 A US 2002143040 A1 US 2002107270 A1 US 2002107271 A1 US 2002198244 A1 US 2002115701 A1 US 2002198245 A1 IL 117003 A	16-08-1999 17-10-1996 29-10-1999 29-09-1997 27-06-1996 27-06-1996 03-07-2001 10-12-1996 15-06-1999 04-10-1996 22-09-1997 07-05-1997 01-09-2000 14-12-1999 26-03-2002 31-08-1999 03-10-2002 08-08-2002 08-08-2002 26-12-2002 22-08-2002 26-12-2002 31-10-2000
WO 9619463	A	27-06-1996	JP 2636819 B2 JP 9052882 A AT 180253 T AU 695045 B2 AU 4189796 A BR 9506815 A CA 2183645 A1 CA 2208316 A1 CA 2341921 A1 CN 1146204 A CZ 9602749 A3 DE 69509753 D1 DE 69509753 T2 DK 745596 T3 EP 0826676 A1 EP 0745596 A1 ES 2132751 T3 FI 963238 A GR 3030643 T3 HU 76541 A2 WO 9619462 A1 WO 9619463 A1 JP 3181190 B2 JP 8325249 A KR 201581 B1 NO 963450 A NZ 297105 A SK 117596 A3 TW 403742 B US 6002014 A US 6362209 B1 US 5994381 A US 5945539 A US 2002143040 A1	30-07-1997 25-02-1997 15-06-1999 06-08-1998 10-07-1996 09-09-1997 27-06-1996 27-06-1996 27-06-1996 26-03-1997 11-12-1996 24-06-1999 02-12-1999 08-11-1999 04-03-1998 04-12-1996 16-08-1999 17-10-1996 29-10-1999 29-09-1997 27-06-1996 27-06-1996 03-07-2001 10-12-1996 15-06-1999 04-10-1996 22-09-1997 07-05-1997 01-09-2000 14-12-1999 26-03-2002 30-11-1999 31-08-1999 03-10-2002

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/06502

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9619463	A	US 2002107270 A1		08-08-2002
		US 2002107271 A1		08-08-2002
		US 2002198244 A1		26-12-2002
		US 2002115701 A1		22-08-2002
		US 2002198245 A1		26-12-2002
		IL 117003 A		31-10-2000
EP 0826676	A 04-03-1998	JP 3181190 B2		03-07-2001
		JP 8325249 A		10-12-1996
		EP 0826676 A1		04-03-1998
		US 5945539 A		31-08-1999
		AT 180253 T		15-06-1999
		AU 695045 B2		06-08-1998
		AU 4189796 A		10-07-1996
		BR 9506815 A		09-09-1997
		CA 2183645 A1		27-06-1996
		CA 2208316 A1		27-06-1996
		CA 2341921 A1		27-06-1996
		CN 1146204 A		26-03-1997
		CZ 9602749 A3		11-12-1996
		DE 69509753 D1		24-06-1999
		DE 69509753 T2		02-12-1999
		DK 745596 T3		08-11-1999
		EP 0745596 A1		04-12-1996
		ES 2132751 T3		16-08-1999
		FI 963238 A		17-10-1996
		GR 3030643 T3		29-10-1999
		HU 76541 A2		29-09-1997
		WO 9619462 A1		27-06-1996
		WO 9619463 A1		27-06-1996
		JP 2636819 B2		30-07-1997
		JP 9052882 A		25-02-1997
		KR 201581 B1		15-06-1999
		NO 963450 A		04-10-1996
		NZ 297105 A		22-09-1997
		SK 117596 A3		07-05-1997
		TW 403742 B		01-09-2000
		US 6002014 A		14-12-1999
		US 6362209 B1		26-03-2002
		US 5994381 A		30-11-1999
		US 2002143040 A1		03-10-2002
		US 2002107270 A1		08-08-2002
		US 2002107271 A1		08-08-2002
		US 2002198244 A1		26-12-2002
		US 2002115701 A1		22-08-2002
		US 2002198245 A1		26-12-2002
EP 0745596	A 04-12-1996	JP 2636819 B2		30-07-1997
		JP 9052882 A		25-02-1997
		AU 695045 B2		06-08-1998
		AU 4189796 A		10-07-1996
		BR 9506815 A		09-09-1997
		CZ 9602749 A3		11-12-1996
		DE 69509753 D1		24-06-1999
		DE 69509753 T2		02-12-1999
		DK 745596 T3		08-11-1999
		EP 0745596 A1		04-12-1996
		FI 963238 A		17-10-1996

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No	
PCT/EP 03/06502	

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
EP 0745596	A		GR 3030643 T3 KR 201581 B1 NO 963450 A SK 117596 A3 US 5994381 A AT 180253 T CA 2183645 A1 CA 2208316 A1 CA 2341921 A1 CN 1146204 A EP 0826676 A1 ES 2132751 T3 HU 76541 A2 WO 9619462 A1 WO 9619463 A1 JP 3181190 B2 JP 8325249 A NZ 297105 A TW 403742 B US 6002014 A US 6362209 B1 US 5945539 A US 2002143040 A1 US 2002107270 A1 US 2002107271 A1 US 2002198244 A1 US 20022115701 A1 US 2002198245 A1 IL 117003 A	29-10-1999 15-06-1999 04-10-1996 07-05-1997 30-11-1999 15-06-1999 27-06-1996 27-06-1996 27-06-1996 26-03-1997 04-03-1998 16-08-1999 29-09-1997 27-06-1996 27-06-1996 03-07-2001 10-12-1996 22-09-1997 01-09-2000 14-12-1999 26-03-2002 31-08-1999 03-10-2002 08-08-2002 08-08-2002 26-12-2002 22-08-2002 26-12-2002 31-10-2000
US 5945539	A	31-08-1999	JP 3181190 B2 JP 8325249 A AT 180253 T AU 695045 B2 AU 4189796 A BR 9506815 A CA 2183645 A1 CA 2208316 A1 CA 2341921 A1 CN 1146204 A CZ 9602749 A3 DE 69509753 D1 DE 69509753 T2 DK 745596 T3 EP 0826676 A1 EP 0745596 A1 ES 2132751 T3 FI 963238 A GR 3030643 T3 HU 76541 A2 WO 9619462 A1 WO 9619463 A1 JP 2636819 B2 JP 9052882 A KR 201581 B1 NO 963450 A NZ 297105 A SK 117596 A3	03-07-2001 10-12-1996 15-06-1999 06-08-1998 10-07-1996 09-09-1997 27-06-1996 27-06-1996 27-06-1996 26-03-1997 11-12-1996 24-06-1999 02-12-1999 08-11-1999 04-03-1998 04-12-1996 16-08-1999 17-10-1996 29-10-1999 29-09-1997 27-06-1996 27-06-1996 30-07-1997 25-02-1997 15-06-1999 04-10-1996 22-09-1997 07-05-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/06502

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 5945539	A	TW US US US US US US US US US	403742 B 6002014 A 6362209 B1 5994381 A 2002143040 A1 2002107270 A1 2002107271 A1 2002198244 A1 2002115701 A1 2002198245 A1	01-09-2000 14-12-1999 26-03-2002 30-11-1999 03-10-2002 08-08-2002 08-08-2002 26-12-2002 22-08-2002 26-12-2002
WO 0145703	A 28-06-2001	AU BR CA CN EP JP WO US US	2592801 A 0017037 A 2393724 A1 1434712 T 1246621 A1 2003523958 T 0145703 A1 2003220228 A1 2001041726 A1	03-07-2001 10-06-2003 28-06-2001 06-08-2003 09-10-2002 12-08-2003 28-06-2001 27-11-2003 15-11-2001
WO 0230866	A 18-04-2002	IT AU CA WO EP	MI20002202 A1 1593202 A 2425649 A1 0230866 A1 1339665 A1	12-04-2002 22-04-2002 18-04-2002 18-04-2002 03-09-2003
WO 9613483	A 09-05-1996	AT AU AU CA WO DE DE EP ES JP US	185797 T 688980 B2 3695095 A 2200462 A1 9613483 A1 69512930 D1 69512930 T2 0788476 A1 2139959 T3 10507765 T 5849943 A	15-11-1999 19-03-1998 23-05-1996 09-05-1996 09-05-1996 25-11-1999 18-05-2000 13-08-1997 16-02-2000 28-07-1998 15-12-1998
EP 0788467	A 13-08-1997	AT AU DE DE EP FI US WO	209166 T 3747395 A 69524118 D1 69524118 T2 0788467 A1 971815 A 5846281 A 9613465 A1	15-12-2001 23-05-1996 03-01-2002 18-07-2002 13-08-1997 28-04-1997 08-12-1998 09-05-1996
US 5849943	A 15-12-1998	AU AU DE DE EP JP AT CA WO ES	688980 B2 3695095 A 69512930 D1 69512930 T2 0788476 A1 10507765 T 185797 T 2200462 A1 9613483 A1 2139959 T3	19-03-1998 23-05-1996 25-11-1999 18-05-2000 13-08-1997 28-07-1998 15-11-1999 09-05-1996 09-05-1996 16-02-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No PCT/EP 03/06502	
---	--

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9911605	A 11-03-1999	AT 237580	T	15-05-2003
		AU 743371	B2	24-01-2002
		AU 9534098	A	22-03-1999
		BR 9812010	A	12-12-2000
		CN 1268112	T	27-09-2000
		DE 69813570	D1	22-05-2003
		DK 1007505	T3	21-07-2003
		WO 9911605	A1	11-03-1999
		EP 1007505	A1	14-06-2000
		JP 2001514244	T	11-09-2001
		NO 20000943	A	25-02-2000
		NZ 502669	A	01-02-2002
		PL 338357	A1	23-10-2000
		RU 2186762	C2	10-08-2002
		SI 1007505	T1	31-10-2003
		SK 2472000	A3	12-09-2000
		TR 200000447	T2	21-07-2000
		US 6291523	B1	18-09-2001
		US 2002183391	A1	05-12-2002
		US 6310099	B1	30-10-2001
		US 2002013369	A1	31-01-2002
		ZA 9807785	A	01-03-1999
		HU 0002514	A2	28-12-2000

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